REMARKS

The Applicants thank the Examiner for the thorough examination of the application. The specification has been amended to add headings and to remove references to the claims. No new matter is believed to be added to the application.

Status of the Claims

Claims 1-19 are pending in the application. Claims 1-13 have been withdrawn from consideration by the Examiner. The amendments to claim 14 find support at page 5, lines 27-30 and at page 6, lines 6-7 of the specification. The amendments to claim 18 find support at page 4, lines 17-18 of the specification. Claim 19 finds support at page 4, lines 1-3 of the specification.

Election/Restriction Requirement

The Examiner has restricted the claims of the application into the following two groups:

Group I, claims 1-13, drawn to a composition comprising a charged active substance bonded to an oppositely bonded chitosan; and

Group II, claim 14, drawn to a method of preparing the composition.

Applicants have elected Group II with traverse. The Examiner has withdrawn claims 1-13 from consideration.

However, the claims of Group I and Group II are drawn to a single general inventive concept under PCT Rule 13.1. PCT Rule 13.2 states that "Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features."

The above-mentioned rules are illustrated in MPEP AI-67 (Examples Concerning Unity of Invention), particularly in Example 1 ("Claim 1: A method of manufacturing chemical substance X. Claim 2: Substance X. Claim 3: The use of substance X as an insecticide. Unity exists between claims 1, 2 and 3. The special technical feature common to all the claims is substance X"). Example 1 of MPEP AI-67 clearly parallels the circumstances of both an active substance and a chitosan derivative being present in both Group I and Group II of the invention.

Also, evidence of the unity of the invention can be found in the International Preliminary Examination Report (PCT/IPEA/409) of November 15, 2001, which was made of record in the instant application on May 23, 2002. The International Preliminary Examination Report considered all of claims 1-14 and found both novelty and an inventive step.

As a result, the unity of the invention is clear.

Accordingly, rejoinder of both groups and examination of all the claims on the merits are respectfully requested.

Objection to the Specification

The Examiner objects to the specification as referring to claim 1. The specification has been amended to not refer to the claims.

Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 14-18 are rejected under 35 U.S.C. §112, second paragraph as being indefinite. Applicants traverse.

In the Office Action, the Examiner inquires whether the final product is in the form of a liquid or solid. Claim 14 has been amended to set forth a "dried nanosol."

Also, the Examiner requested clarification of the terms "sol" and "nanosol." A "sol" is the more general term which refers to all kinds of colloidal dispersions, whereas the term "nanosol" refers to the type of sol as defined inn DE 41 40 195. This type of sol is obtained by following steps a to c of the process of claim 14 (step d is only a drying step which converts the aqueous sol into a solid preparation). After adjusting the pH as described in step c, a nanosol in accordance with the present invention is obtained. Page 2, last paragraph of the specification describes that in "nanosols" the active substance is stabilized in an isoionic state with the carrier, and this is the case after step c of claim 14 is completed.

Therefore, the term "sol" is correctly used in steps b and c of claim 14, and the term "nanosol" is correctly used in step d.

Claim 14 has also been amended to add the words "and the active substance" to clarify that the aqueous sol contains both the chitosan derivative and the active substance.

Also, claim 18 has been rewritten to clearly set forth that further polymeric substance is added apart from the chitosan derivative.

As a result, the claims are clear, definite and have full antecedent basis. This rejection is accordingly overcome and withdrawal thereof is respectfully requested.

Rejections Under 35 U.S.C. §103(a)

Claims 14 and 16-18 are rejected under 35 U.S.C. §103(a) as being obvious over Illum (U.S. Patent 5,863,554) in view of Wunderlich (U.S. Patent 5,932,245) and Roy (U.S. Patent 5,972,707). The Examiner adds Shinetsu (JP-211903) to the aforesaid rejection to reject claims 14-18. Applicants respectfully traverse.

The Present Invention and its Advantages

The present invention pertains to a novel pharmaceutical preparation containing an active substance and a chitosan derivative. The present invention finds a typical embodiment in claim 14, which sets forth:

> 14. A process for the production of a solid pharmaceutical preparation comprising at least one at least partially charged active substance, which active substance is present in the form of a dried nanosol in which the active substance is bonded to an oppositely charged chitosan derivative, which comprises:

a) selecting a chitosan derivative according to the type and relative number of its charged groups and in coordination with the type and relative number of the charged groups of the active substance such that at a certain pH value an isoionic state or charge equalization between active substance and carrier can be achieved in the preparation,

b) preparing an aqueous sol containing the active substance from the chitosan derivative and the active substance,

c) adjusting the pH value of the aqueous sol such that an isoionic state results, possibly with colloidal or nano-scale active substance particles precipitating, and

d) drying the thus-obtained aqueous nanosol.

The pharmaceutical agent of the invention can be used in the production of medicinal agents that are administered in the form of capsules, tablets, powders or granulates, and can be dissolved or re-dispersed in water or another suitable liquid prior to being administered.

Distinctions of the Invention Over the Cited Art

Illum pertains to a drug delivery system that includes microspheres. Illum fails to teach the preparation of nanosol, as is admitted by the Examiner.

Illum discusses chitosan microspheres that are produced by an emulsion technique (col. 7, lines 36-46). According to Illum's technique, an aqueous solution of chitosan is emulsified with soybean oil. In this emulsion, the aqueous chitosan forms tiny droplets which are suspended in the oil phase. By cross-linking, these droplets are stabilized to produce the microspheres. Drug substances may be incorporated either during the emulsification process into the

emulsion droplets. Or afterwards into the solidified microspheres (col. 7, lines 47-49).

Wunderlich pertains to a process for making nanosols by using proteins such as gelatin or collagen. Wunderlich fails to teach the use of carbohydrates, particularly chitosan derivatives.

In contrast, the invention pertains to a process that is fundamentally different from the process described in Illum and Wunderlich. In particular, the process described by Illum does not have a step of preparing an aqueous sol that contains a chitosan derivative and an active substance (step b of instant claim 14). Instead, Illum teaches the preparation of an emulsion, which is clearly not a sol. Illum further fails to teach pH adjustment, particularly pH adjustment of an aqueous sol containing a chitosan derivative and an active substance (step c of instant claim 14).

The products obtained by the process of Illum are also fundamentally different from the nanosol particles of the present invention. In the nanosol particles of the present invention, the active substance is bonded to an oppositely charged chitosan derivative. Illum fails to teach such bonding. Rather, the active agent is "incorporated" or "sorbed into" the microspheres (col. 7, lines 47-49). Also, the large microspheres obtainable by the Illum process cannot be considered equivalent to the small inventive nanoparticles. Illum at column 7, lines 45-46 describes a size of 10-90 μm. In contrast, the specification at page 4, line 3 has an average particle size "at maximum 500-1000 nm." See claim 19.

At page 5, lines 10-11 of the Office Action, the Examiner asserts: "Illum had taught that chitosan and gelatin are functional equivalents in the delivery of therapeutic agents having problematic availability." However, this conclusion cannot be applied to the Wunderlich process. Illum does discuss that chitosan and gelatin are functional equivalents when preparing microspheres by the emulsion technique described by Illum. However, as explained above, this emulsion technique and the microspheres obtained by this technique are fundamentally different from the nanosol process and the nanosol preparation of the present invention (and also from the nanosol process and nanosol particles described by Wunderlich).

Also, in the Examiner's statement "chitosan and gelatin are functional equivalents in the delivery of therapeutic agents having problematic availability," the concept of "problematic availability" has no relevance in the question of whether or not a certain component (chitosan) which is useful in an emulsion process might also be useful for a completely different manufacturing process (nanosol technique).

As a result, one having ordinary skill would have no motivation to combine the teachings of Illum and Wunderlich.

Roy describes nanospheres that result from combining a polymeric cation (which is a carbohydrate, e.g. chitosan) and a polyanion (a nucleic acid as in claim 1 of Roy). These nanospheres are obtained by a well-known coacervation process (col. 5, line 66 to col. 6, line 7) in which two polymers of opposite charge (DNA,

chitosan) form complexes as a result of the desolvation of the local water environment of the charged polymers. To induce this desolvation, certain salts (sodium sulfate) or ethanol must be added (col. 4, lines 46-51, and 62-67; col. 5, line 66 to col. 6 line 7; Example 3, col. 10, lines 11-15; claims 10, 11 and 12). Also, Roy discusses chitosan and not chitosan derivatives.

The present invention of claims 14-18 clearly do not pertain to a coacervation process. The process of the present invention does not require the presence of two oppositely charged polymers (the active substance is usually a low molecular weight drug). Nanosol formation is induced by pH adjustment. In contrast, the process of Roy forms a coacervate by adding a salt or ethanol.

The coacervation method is therefore based on a completely different principle, as compared to nanosol formation. One having ordinary skill would therefore have no motivation to combine Roy with the nanosol technology of Wunderlich.

At page 5, lines 13-16 of the Office Action, the Examiner asserts: "One of ordinary skill would reasonably expect success in using the Wunderlilch process to prepare nanosols using chitosan because Roy has demonstrated that chitosan is at least equivalent to . . . gelatin for the preparation of nanospheres." However, as noted above, Roy had only demonstrated that chitosan is equivalent to gelatin in a coacervation process. Since coacervation is based on a completely different reaction principle as compared too nanosol formation (as in Wunderlich), one

having ordinary skill would have no motivation to expect success if Roy is combined with Wunderlich.

Both the cited references of Illum and Roy describe the use of chitosan in process that are fundamentally different from the nanosol technique of the Wunderlich process and also from the nanosol process of instant claim 14. Therefore, one having ordinary skill would not expect that chitosan derivatives could be used in a process for making active substance-containing nanosols. Further, Wunderlich's teachings are restricted to the use of proteins such as gelatins or collagen hydrolysates (col. 15, lines 4-5, 19-23). Therefore Wunderlich provides no motivation for using carbohydrates such as chitosan derivatives.

As a result, one having ordinary skill in the art would not combine Illum, Wunderlich and Roy to produce the invention embodied by independent claim 14. A *prima facie* case of obviousness has thus not been made. Claims dependent upon claim 14 are patentable for at least the above reasons.

The Examiner turns to Shinetsu for teachings pertaining to sulfated chitosan, a zwitterionic acidic chitosan derivative. However, Shinetsu fails to address the inability to combine Illum, Wunderlich and Roy to allege *prima facie* obviousness.

These rejections are accordingly overcome and withdrawal thereof is respectfully requested.

Information Disclosure Statements

The Examiner is respectfully requested to consider the Information Disclosure Statements filed January 7, 2003 and to make the initialed PTO-1449 form of record in the application in the next official action.

The Examiner is thanked for considering the Information Disclosure Statement filed February 26, 2002 and for making the initialed PTO-1449 form of record in the application in the Office Action mailed February 12, 2004.

Foreign Priority

The Examiner has acknowledged foreign priority in the Office Action mailed February 12, 2004.

Conclusion

If there are any questions concerning this Amendment, the Examiner is respectfully requested to contact Robert E. Goozner, Ph.D. (Reg. No. 42,593) at the telephone number below to arrange an interview.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
James M. Slattery, #28,380

JMS/REG:jls
3868-0109P

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000